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Prognostic Significance of Surgical Margin in Hepatocellular Carcinoma Resection: An Analysis of 165 Childs' A Patients

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Background and Objectives: The clinical significance of the width of the surgical margin in the resection of hepatocellular carcinoma (HCC) has yet to be clarified.

Methods: Childs' A patients (165) who underwent resections of HCC were studied. Patients were divided into a wide margin group (1.0 cm or more, group W, n = 85), and a narrow margin group (<1.0 cm, group N, n = 80).

Results: Multivariate analysis showed that preoperative α-fetoprotein level ($P = 0.0202$), venous invasion ($P = 0.0226$), surgical margin ($P = 0.0012$), and TNM stage ($P = 0.0023$) were significant predictors of disease-free survival. By the log-rank test, the disease-free survival rate of the group W patients was significantly higher than that of the group N patients ($P = 0.0007$). Group N had a higher percentage of patients undergoing minor resection (wedge resection or subsegmentectomy) (44% vs. 26%, $P = 0.016$) and had a higher percentage of patients with centrally located tumor (62% vs. 29%, $P = 0.000$) than group W.

Conclusions: The results of this study indicated the significant influence of surgical margin on HCC recurrence after resection. Minor resection and centrally located tumor are factors related to a narrow surgical margin.

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KEY WORDS: surgical margin; hepatocellular carcinoma resection; prognostic factors; tumor location; extent of resection

INTRODUCTION

Surgical resection is now the treatment of choice for primary hepatocellular carcinoma (HCC). Like some other cancers, the biological features of the primary lesion of HCC affect the postresectional prognosis. Some of these factors include preoperative α-fetoprotein level [1,2], tumor size [3,4], tumor number [5], capsular formation [4], and venous invasion [4,6]. In addition to these biological factors, it has been proposed that some surgical factors, such as intraoperative blood transfusion [7], intraoperative tumor dissemination [8,9], and anatomical resection [10–12], might be related to the postresectional outcome.

Surgical margin is another surgical factor that is being evaluated for its prognostic significance. The surgical margin of resected HCC represents the shortest distance between the section line and the tumor margin. An adequate margin had been defined by Lee et al. [13] as a margin exceeding or equal to 1.0 cm. Although this criteria has been widely adopted by hepatic surgeons, its prognostic significance remains controversial, according to the results of several recently reported series [14–19].

In this study, we measured the surgical margin of the resected specimen in 165 HCC patients with Childs' A liver function, who underwent hepatic resection at the same institution by a hepatic surgical team. The prog-

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nostic significance of the margin was evaluated using multivariate analysis. Clinicopathological factors related to a narrow surgical margin of HCC resection were also investigated.

MATERIALS AND METHODS

Patients

Between July 1991 and August 1995, 201 patients with HCC underwent hepatectomy at Veterans General Hospital-Taipei, Taiwan. All the patients had the tumor tissue completely removed macroscopically during operation. According to the classification of Child modified by Pugh et al. [20], 165 patients (82%) had a liver function belonging to class A, 31 (15%) to class B, and 5 (3%) to class C. In view of the potential influence of patients' liver functional status on postresectional prognosis [21,22], the patients entered into this study are confined to the 165 Childs' class A cases.

The study comprised 142 men and 23 women with a mean age of 58 years (range, 20–83 yr). Twenty-six (16%) patients had received preoperative transcatheter arterial chemoembolization, which consisted of injection of oily contrast medium (Lipiodol, Laboratoire Guerget, Aulnay-sous-Bois, France) mixed with 25–30 mg of epirubicin hydrochloride (Pharmorubicin, Farmitalia Carlo Erba Research Laboratories, Milan, Italy), followed by injection of gelatin sponge particles (Spongostan, Ferrisan, Copenhagen, Denmark) into the hepatic artery.

The types of hepatic resection included 57 minor resections (defined as wedge resection in 34 patients, subsegmentectomy in 23), and 108 major resections (segmentectomy in 40 patients, lobectomy in 62, and extended lobectomy in 6). Segmentectomy indicates resection of one of the four segments (posterior, anterior, medial, or lateral) of the liver as classified by Healey and Schroy nomenclature [23]. Subsegmentectomy indicates resection of a Couinaud's segment [24]. Wedge resection indicates nonanatomic resection.

Patient preoperative liver function evaluation included serum biochemical study, measurement of prothrombin time, and testing of indocyanine green retention rate at 15 minutes. Preoperative image study for tumor staging included a routine chest X-ray, abdominal ultrasonography, computed tomography, hepatic arteriography (including indirect arterial portography), and magnetic resonance imaging, if indicated.

Procedures

The operative procedures have been described elsewhere [3,25,26]. We performed intraoperative ultrasonography on all patients. In 49 patients (30%), vascular inflow occlusion at the hilus was done. The hepatic parenchyma was transected using either a small Kelley clamp (tissue-fracture technique) or an ultrasound dissector. During parenchymal transection, attempts were made to keep a surgical margin of 1 cm or more in width in each case.

After the surgical procedure, the resected specimens were examined meticulously by the surgeons and the pathologist (S.H.T). The specimens were cut into slices ~10 mm thick. The macroscopic features of the tumor, including tumor size, tumor number, capsular formation, and tumor venous invasion were recorded. A detailed measurement of the surgical margin was done before the specimen was fixed in 10% formalin. The surgical margin was measured as the shortest distance from the tumor edge to the limit of parenchymal resection. When the surgical margin was <1.0 cm, it was classified as a narrow surgical margin; when it was 1.0 cm or more, it was classified as a wide surgical margin. We defined the tumor's location as central type when it was <3.0 cm from the portal main bifurcation and as peripheral type when it was 3.0 cm or more from the bifurcation. These shortest distances of the tumor to the bifurcation were obtained from preoperative image study (CT portography and indirect arterial portography) and intraoperative ultrasonography. HCC was graded for histological differentiation according to the Edmondson-Steiner classification [27]. The tumor stage was evaluated according to the International Union Against Cancer (UICC) TNM classification [28].

DNA ploidy, analyzed with fresh tissue samples, was measured with a flow cytometer (Epics Profiles, Coulter Electronics, Hialeah, FL) as previously described [29]. The ploidy status was defined as diploid (2N) when the G0/G1 peak was superimposed after the addition of human peripheral blood lymphocytes to the samples with a range from 1.9N to 2.1N. Aneuploid was defined if the discrete G0/G1 peak or peaks were outside the diploid range (1.9N–2.1N).

Patients were followed up every 2 months with measurement of serum α-fetoprotein level, ultrasonography, and/or computed tomography or magnetic resonance imaging. At any suspicion of a recurrence, an angiographic examination was carried out. Diagnosis of intrahepatic tumor recurrence was made when at least two of those five modalities were interpreted as positive findings. Disease-free survival was measured from the date of hepatic resection to the date when recurrence of HCC was diagnosed or, in the absence of detectable tumor, to the date of death or last follow-up.

Statistics

The data were analyzed using a statistical package program (SPSS Statistical Software, Chicago, IL) [30]. Statistical analysis was performed using the Chi-square test, Fisher's exact test, and two-tailed Student's *t*-test as appropriate. Survival rates were calculated using the Kaplan-Meier method [31], and survival curves were compared using the log-rank test. Independent prognostic

TABLE I. Results of Univariate and Multivariate Analysis of Prognostic Factors of Disease-Free Survival After Resection of HCC

Variables	Categorization	*P* value	
		Univariate	Multivariate
Sex	male, female	0.6846	0.4141
Age (yr)	⩽65, >65	0.8777	0.3528
Hepatitis B surface antigen	positive, negative	0.7743	0.6199
ICG-15′ (%)[a]	⩽10, >10	0.1484	0.0870
α-fetoprotein level (ng/ml)	⩽200, >200	0.0028*	0.0202*
Liver cirrhosis	presence, absence	0.2379	0.2814
Tumor number	solitary, multiple	0.0000*	0.7733
Tumor size (cm)	⩽3.0, >3.0	0.0102*	0.7255
Venous invasion	presence, absence	0.0006*	0.0226*
Surgical margin (cm)	<1.0, ⩾1.0	0.0007*	0.0012*
DNA ploidy	diploid, aneuploid	0.8966	0.6504
TNM stage	I, II, III, IVa	0.0000*	0.0023*

[a]Indocyanine green retention rate at 15 minutes (normal values are 0–10%).
*Statistically significant.

variables were evaluated by Cox multivariate proportional hazard model. All data were expressed as means ± SD. Any *P* values <0.05 were considered to be statistically significant.

RESULTS

By univariate analysis, significant prognostic factors were preoperative α-fetoprotein level, tumor number, tumor size, venous invasion, surgical margin, and TNM staging. The result of Cox multivariate proportional hazard model indicated that preoperative α-fetoprotein level, venous invasion, surgical margin, and TNM staging were significant predictive factors of disease-free survival after HCC resection (Table I).

Among these 165 patients, 86 patients (52%) had cirrhosis of the liver. Eighty-five patients (52%) had the tumors resected with a surgical margin of 1.0 cm or more in width (group W, wide surgical margin group). Eighty patients (48%) had a surgical margin of <1.0 cm (group N, narrow surgical margin group). A comparison of all the preoperative and demographic characteristics of the two groups showed the only significant variable to be that Group N had a higher percentage of patients undergoing minor resection (44% vs. 26%, $P = 0.016$) and a higher percentage of patients with centrally located tumors (62% vs. 29%, $P = 0.000$) than group W. A minor resection, therefore, was more likely to be treated with a smaller resection margin.

All patients had been followed for at least 14 months. During follow-up, intrahepatic and/or extrahepatic recurrence of the tumor had been confirmed in 85 patients. The mean interval for tumor recurrence after resection was 11.7 months (range 2.0–47.2 months). Table II lists the patterns of tumor recurrence in the two groups. The incidence of intrahepatic recurrence in the segment near the resected stump was significantly higher in group N (55%) than in group W (29%) patients ($P = 0.022$). Overall, the disease-free survival rates of the 165 patients were 67% at 1 year, 47% at 3 years, and 37% at 5 years after operation, respectively. By log-rank test, the disease-free survival rates of group W were significantly higher than those of group N ($P = 0.0007$) (Fig. 1).

TABLE II. Pattern of Recurrence in Patients With Wide and Narrow Surgical Margin

Site of recurrence	Wide surgical margin (⩾1.0 cm) (n = 85)	Narrow surgical margin (<1.0 cm) (n = 80)
Extrahepatic[a]	13	10
Lung	8	7
Bone	6	2
Skin	0	2
Brain	1	1
Intraabdomen	3	3
Intrahepatic	31	49
same/adjacent segment	9*	27*
nonadjacent segment	13	12
both	9	10

[a]Some patients had more than one extrahepatic recurrent site.
*$P < 0.05$.

DISCUSSION

The results of this multivariate analysis confirmed the prognostic significance of surgical margin being an independent predictive factor of disease-free survival in HCC resection. Other independent predictors are preoperative α-fetoprotein level, venous invasion, and TNM staging.

Some features of HCC may be the pathological evidence supporting the prognostic significance of surgical margin in HCC resection. 1. HCC is characterized by intrahepatic metastasis (e.g., venous invasion and daugh-

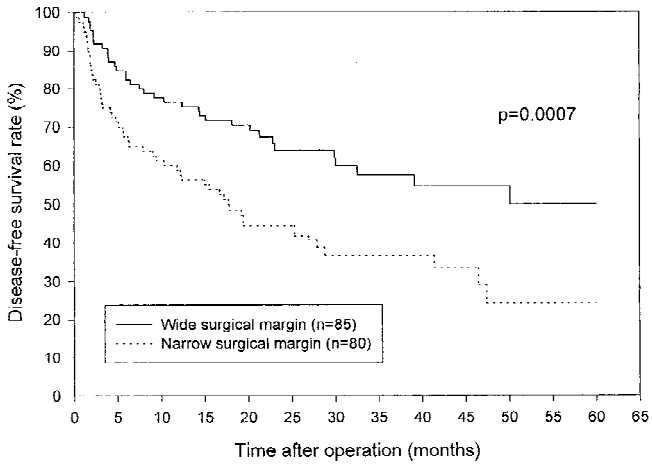

Fig. 1. Comparison of disease-free survival after HCC resection between patients with wide surgical margin (⩾1.0 cm) and patients with narrow surgical margin (<1.0 cm). Survival in the wide surgical margin group is significantly better than that in the narrow surgical margin group (log-rank test, $P = 0.0007$).

ter nodule formation) [25], and early metastasis is usually limited to the vicinity of the primary lesion [32–34]. 2. Small HCCs may have indistinct margins, which is sometimes difficult to determine during parenchymal transection, especially in liver with a cirrhotic background [35,36]. 3. With the hypothesis of a stepwise progression of carcinogenesis, some HCCs have been found to be associated with the cancerous areas of well-differentiated tumors around the main nodule [37,38]. These surrounding cancerous areas went undetected by the perioperative radiological and macroscopical examinations. Accordingly, a wide surgical margin provides a chance of histological tumor clearance along the parenchymal transection line. This is also reflected by our findings that patients with a wide surgical margin had a lower incidence of intrahepatic recurrence near the resected hepatic stump as compared with patients with a narrow margin.

Although a macroscopic margin of 1.0 cm is regarded as adequate for cure as originally proposed by Lee et al. [21], this margin may fail to ensure disease clearance when intrahepatic tumor involvement is extensive. Whether further extension of margin has additional prognostic benefits is still in dispute. Tang et al. [39] had advocated a larger margin of 2–3 cm for all patients with small tumors [39]. Furukawa et al. [40] had reported that for HCC <5 cm in size, patients with a surgical margin of 2.0 cm or more had a disease-free survival rate significantly better than those with a margin <2.0 cm [40], whereas in a study of 65 HCC patients with tumor size >5.0 cm, Lai et al. [41] indicated that further extension of margin had no additional prognostic benefit. In this study, we found that there is no significant difference in disease-free survival rate between patients with surgical margins ranging between 1.0–2.0 cm and patients with margin >2.0 cm (by log-rank test, $P = 0.9681$).

In our series, despite attempts to keep a surgical margin of 1 cm or more in width in each case, only 52% patients had the tumors successfully resected with a surgical margin of 1.0 cm or more. These data are compatible with those of previous reported series, i.e., that 20–88% of the resection can achieve a 1.0 cm clearance of surgical margin [2,18,19]. In this study, we found that extent of resection and tumor location were determinants that govern the extent of surgical margin.

Previously, no definite criteria concerning tumor location and superficiality has been made. In this study we found that stratification of tumor into central type (<3.0 cm from the portal main bifurcation) and peripheral type (3.0 cm or more from the bifurcation) is an effective method to estimate tumor location and superficiality. These data are potentially available before exploration by imaging studies and can be included in HCC patients' preoperative evaluation, in addition to the routine liver function test and tumor staging. When tumors are of a peripheral type and located superficially, adequate resection with a wide margin can be achieved even when the tumor has extended to adjacent organ(s) [26]. Deep resection from the liver surface for a central type tumor is anatomically restricted by the hilar structures, including portal and bile duct pedicles as well as the main trunks of hepatic veins. For a centrally located tumor, it is difficult to resect the tumor adequately with a minor resection. Consequently, our outlook is that patients with centrally located tumors deserve to be treated with a major resection as long as the operation is within the safe limit of hepatic functional reserve [3,25].

During liver parenchymal transection, some technical aspects are important in order to achieve a potential obtainable surgical clearance margin. Since the structure of the liver is somewhat like an inverted cone and HCC has both a radial and vertical growth phase, a wide transverse margin does not necessarily guarantee an adequately deep margin. Accordingly, during parenchymal transection, the actual status of the surgical margin of the tumor should be monitored diligently using intraoperative sonography, and a clean intraparenchymal operative area should be maintained. These maneuvers are helpful in keeping the liver parenchyma divided in a correct direction. In 1993, Izumi et al. [42] proposed a technique of inserting needles along the transection plane to guarantee an adequate transection of the liver. Recently, Fan et al. [43] reported that using an ultrasonic dissector during parenchymal dissection was helpful to obtain a wider margin than using the crushing and finger fracture techniques, presumably due to the fact that ultrasonic dissector allows precise division of the liver along the plane determined by intraoperative ultrasonography, especially at the deeper portions of the transection plane.

In summary, the result of this multivariate analysis indicated that a narrow surgical margin is a significant risk factor of recurrence of HCC after hepatectomy. Minor resection and centrally located tumors are factors related to a narrow surgical margin. Accordingly, in addition to routine staging of the tumor, a prediction of an obtainable surgical margin should be included in the preoperative evaluation of HCC patients. This procedure is helpful in order to establish an appropriate treatment modality for the patients.

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